Treatment patterns and distribution of low-density lipoprotein cholesterol levels in treatment-eligible United States adults

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Abstract:

To estimate the fraction of United States (U.S.) adults who are eligible for treatment to reduce elevated low-density lipoprotein (LDL) cholesterol levels based on Adult Treatment Panel II (ATP II) guidelines and the percent reduction in LDL cholesterol required by those who qualify for treatment, we analyzed data on 7,423 respondents to Phase 2 of the third National Health and Nutrition Examination Survey (NHANES III) administered between 1991 and 1994. Approximately 28% of the U.S. adult population aged ≥20 years is eligible for treatment based on ATP II guidelines. Eighty-two percent of adults with coronary heart disease are not at their target LDL cholesterol level of 100 mg/dl. Of those eligible for treatment, 65% report that they receive no treatment. Overall, 40% of people who qualify for drug therapy require an LDL cholesterol reduction of >30% to meet their ATP II treatment goal. Approximately 75% of those with coronary heart disease who qualify for drug therapy require an LDL cholesterol reduction of >30%. Although elevated LDL cholesterol levels can be treated, prevalence rates in the U.S. adult population remain high. Several recent studies indicate that a considerable percentage of people treated with drug therapy do not reach their treatment goals. The findings in this study provide at least a partial explanation for why many patients receiving therapy do not reach their treatment goals: they require a larger reduction in LDL cholesterol than many therapies can provide.

Keywords: low-density lipoprotein LDL cholesterol | treatment | Adult Treatment Panel II (ATP II) | coronary heart disease

Article:

In this study, we use recently obtained data from Phase 2 of the third National Health and Nutrition Examination Survey (NHANES III) to address the following questions: (1) What fraction of the United States (U.S.) adult population aged ≥20 years is eligible for treatment to

lower low-density lipoprotein (LDL) cholesterol based on the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel or ATP II) guidelines? (2) What fraction of the eligible population reports that it receives treatment? (3) What is the percent reduction in LDL cholesterol required by those who qualify for drug intervention to reach their LDL cholesterol goals as prescribed by ATP II? We believe that answers to these questions will provide important information regarding current lipid management, which in turn can assist in developing effective intervention strategies to attain the goals outlined by ATP II.

Methods

The analyses in this study are based on data from Phase 2 of the NHANES III survey, which was conducted from 1991 to 1994. NHANES III is the seventh in a series of national surveys started in 1960 and was conducted from October 1988 to October 1994. NHANES III sampled 39,695 persons aged ≥2 months, of whom 31,311 (79%) completed both the survey questionnaire and a physical examination. Phase 2 of NHANES III was conducted from September 1991 to October 1994. In Phase 2, 15,427 persons completed both the survey and the physical examination, of whom 8,588 were aged ≥20 years.[1]

One of the goals of the NHANES III survey is to estimate the national prevalence of diseases and risk factors. Thus, patients were asked about history of diseases, such as systemic hypertension, diabetes mellitus, and heart attack, as well as about risk factors, such as current and past cigarette use. The NHANES III survey also measured total cholesterol, high-density lipoprotein cholesterol, and serum triglycerides for all examinees ≥4 years.

The NHANES III Phase 2 data were recently released publicly. In estimating the prevalence of elevated LDL cholesterol levels, it is important to use the most recent data available because cholesterol screening and treatment patterns have been changing rapidly. For example, the ATP II recommendations were released in 1993, coinciding with the NHANES III Phase 2 survey period of 1991 to 1994. Furthermore, cholesterol-lowering drug therapy has also changed rapidly with the introduction of new statin drugs. Thus, results from the NHANES III Phase 2 data will further enhance our understanding of current lipid levels and management.

In our analysis, we used NHANES III Phase 2 data to determine the fraction of the population aged ≥20 years eligible for treatment according to the ATP II guidelines. ATP II treatment recommendations are listed in Table I.[2] Within this analysis, a person is considered eligible for treatment if he/she belongs to 1 of the following 3 risk groups: (1) has coronary heart disease and an LDL cholesterol level >100 mg/dl; (2) does not have coronary heart disease, has ≥2 risk factors, and an LDL cholesterol level ≥130 mg/dl; or (3) does not have coronary heart disease, has < 2 risk factors, and has an LDL cholesterol level ≥160 mg/dl. Even though ATP II recommends a treatment target LDL cholesterol level of 160 mg/dl for people without coronary heart disease and < 2 risk factors, the guidelines also state that an LDL cholesterol level of <130 mg/dl is considered desirable for everyone without coronary heart disease.

The LDL cholesterol level for each individual was calculated from their total cholesterol, high-density lipoprotein cholesterol, and triglycerides based on the following formula: LDL cholesterol = total cholesterol ─ high-density lipoprotein cholesterol ─ (triglycerides/5).

TABLE I Coronary Heart Disease Risk Groups Based on Adult Treatment Panel II Treatment Recommendations

Coronary Heart Disease Risk Group	LDL Cholesterol to Initiate Diet (mg/dl)	LDL Cholesterol to Initiate Drug (mg/dl)	LDL Cholesterol Goal (mg/dl)
Without coronary heart disease and with <2 risk factors*	≥160	≥190	<160
Without coronary heart disease and with ≥2 risk factors*	≥130	≥160	<130
With coronary heart disease	>100	≥130	≤100

*Positive risk factors for coronary heart disease include age (≥45 for men; ≥55 or premature menopause for women), family history of premature coronary heart disease, current cigarette smoking, hypertension, low high-density lipoprotein cholesterol (<35 mg/dl), and diabetes mellitus. High high-density lipoprotein cholesterol (≥60 mg/dl) is a negative risk factor.

Source: Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Summary of the second report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel II). *JAMA* 1993;269:3015–3023.

This formula, known as the Friedewald equation, was used by the NHANES III to calculate LDL levels for respondents who fasted. To increase sample size, we also applied this formula to nonfasting respondents. Because the formula is not accurate for triglyceride levels >400 mg/dl, we excluded subjects with triglyceride levels >400 mg/dl from our analysis (269 observations excluded). We defined the presence of coronary heart disease as a positive response to the Rose Questionnaire for angina pectoris or a positive response to the question: Has a doctor ever told you that you had a heart attack? Family history of premature coronary heart disease was based on respondents reporting that a first-degree blood relative had a heart attack before age 50. Current cigarette use was defined as a positive response to the question: Do you smoke cigarettes now? We classified respondents as hypertensive if they reported being told by a physician ≥2 times that they had high blood pressure, had been told to take antihypertensive medication, or had ≥2 observed blood pressure readings ≥140/90 mm Hg (systolic ≥140 or diastolic ≥90 mm Hg). We defined the presence of diabetes mellitus as a positive response to the question: Have you ever been told by a doctor that you have diabetes or sugar diabetes?

Diagnosis of high cholesterol was defined as a positive response to the question: Have you ever been told by a health professional that you have high cholesterol? We defined those currently eating fewer high-fat or high-cholesterol foods, controlling weight or losing weight, or exercising on the advice of a health professional to be under dietary therapy. Anybody taking prescribed medicine to lower cholesterol was defined as being under drug therapy.

TABLE II Percentage of U.S. Adults* Who Qualify for Treatment Under Adult Treatment Panel II Guidelines

	Qualify for Treatment		
	Dietary Therapy Alone (%)	Drug Therapy† (%)	Total (%)
All	16.4	11.8	28.2
Race			
White	17.2	11.8	29.0
Black	12.4	12.1	24.5
Race/ethnicity			
Mexican-American	10.8	7.4	18.2
Non-Hispanic black	12.5	12.2	24.7
Non-Hispanic white	17.7	11.8	29.5
Men (age)	17.6	12.8	30.3
20–44	11.5	7.2	18.7
45–54	26.9	22.1	48.9
55–64	26.3	21.1	47.4
65–74	26.0	19.7	45.7
75+	25.1	18.5	43.6
Women (age)	15.3	10.8	26.1
20–44	9.3	2.8	12.2
45–54	17.9	10.2	28.1
55–64	26.4	24.3	50.7
65–74	26.5	27.3	53.8
75+	23.7	29.1	52.8

*≥20 years.
†Subjects who qualify for drug therapy also qualify for dietary therapy.

Following the recommendation of the NHANES III Phase 2 public use file documentation, we excluded 38 subjects with unreliable interviews. We excluded 269 persons with triglyceride levels >400 mg/dl, 350 with missing triglyceride levels, and 29 with missing high-density lipoprotein levels. Finally, we excluded 479 subjects with missing information on risk factors needed to classify treatment eligibility, yielding a total analysis sample of 7,423 persons. All estimates were weighted by the examination sample weights contained in the NHANES III Phase 2 public use file to produce nationally representative estimates for the period 1991 to 1994. Given the relatively high response rate for NHANES III as a whole and the surveys nationally representative sampling frame, we are confident that our results are nationally representative. All results were calculated using SAS 6.11[3] statistical software.

TABLE III U.S. Population by Coronary Heart Disease Risk Group: Number and Percentage Not Meeting Goals

	Coronary Heart Disease Risk Group		
	Without Coronary Heart Disease		With Coronary Heart Disease (treatment goal ≤100 mg/dl)
	<2 Risk Factors (treatment goal <160 mg/dl)	≥2 Risk Factors (treatment goal <130 mg/dl)	
Estimated number in risk group (millions)	121.1	48.7	10.2
Not meeting treatment goals			
Estimated number (millions)	15.7	26.6	8.4
Percentage of risk group	12.9%	54.6%	82.5%
Qualify for dietary therapy alone			
Estimated number (millions)	11.0	15.6	2.9
Percentage of risk group	9.1%	32.1%	28.3%
Qualify for drug therapy*			
Estimated number (millions)	4.7	11.0	5.5
Percentage of risk group	3.8%	22.6%	54.2%
Not meeting desirable level of 130 mg/dl			
Estimated number (millions)	44.6	26.6	NA
Percentage of risk group	36.8%	54.6%	NA

*People who qualify for drug therapy also qualify for dietary therapy.
NA = not applicable.

Results

Prevalence in the U.S. adult population: In Table II, we show the percentage of U.S. adults who qualify for intervention under the ATP II guidelines by race, ethnicity, sex, and age. Overall, 28.2% (50.7 million people) of Americans aged ≥20 are eligible for treatment based on observed LDL cholesterol levels; 16.4% (29.5 million) qualify for dietary therapy alone, and 11.8% (21.2 million) qualify for drug therapy. About 24% of blacks are eligible for treatment, compared with 29% of whites, and about 30% of males are eligible for treatment versus about 26% of females.

Table III shows the estimated number and percentage of U.S. adults aged ≥20 who are not meeting ATP II treatment goals as well as desired LDL cholesterol levels of <130 mg/dl by coronary heart disease risk group. The treatment goal differs from the desired level only for people without coronary heart disease and <2 risk factors. Of those with coronary heart disease, 82.5% are not meeting ATP II treatment goals, and 54.2% qualify for drug therapy. Among U.S. adults without coronary heart disease and with ≥2 risk factors, 54.6% are not meeting ATP II treatment goals, and 22.6% qualify for drug therapy. About 37% of U.S. adults without coronary heart disease and with <2 risk factors are not at the desirable LDL cholesterol level of <130 mg/dl, and 12.9% are not meeting the ATP II treatment goals. About 4% of people in this risk group qualify for drug therapy. If we examine adults without coronary heart disease as a group, 41.9% (71.2 of 169.9 million) are not meeting their desirable LDL cholesterol level of <130 mg/dl. Of those who qualify for drug therapy, 78% (16.5 of 21.2 million) have coronary heart disease or at least 2 coronary heart disease risk factors.

Treatment of elevated low-density lipoprotein cholesterol levels: Table IV shows the estimated number and percentage of the U.S. adult population qualifying for treatment who

report that they are receiving dietary and drug therapy to lower their LDL cholesterol by risk group and treatment eligibility. Among those eligible for treatment based on observed LDL cholesterol levels, 29.0% report that they receive dietary therapy only, and 6.1% report that they receive drug therapy. Sixty-five percent report that they receive no treatment. The percentage of persons who report that they receive dietary therapy alone is actually highest for those with no coronary heart disease and <2 risk factors. Among patients with coronary heart disease who are eligible for treatment, 29.0% report that they receive dietary therapy only, and 12.7% report that they receive drug therapy. Thus, even in this high-risk subgroup, more than half of the respondents report that they do not receive any treatment to lower their LDL cholesterol levels.

TABLE IV Treatment-Eligible Population Receiving Therapy by Risk Group and Treatment Eligiblity

	No Coronary Heart Disease									
	<2 Risk Factors			≥2 Risk Factors			Coronary Heart Disease			
	Diet Eligible	Drug Eligible	All Eligibles	Diet Eligible	Drug Eligible	All Eligibles	Diet Eligible	Drug Eligible	All Eligibles	All Treatment Eligible
Estimated number (million)	11.0	4.7	15.7	15.6	11.0	26.6	2.9	5.5	8.4	50.7
Receiving dietary therapy										
Estimated number (million)	3.3	1.9	5.2	3.7	3.3	7.0	0.7	1.8	2.4	14.7
Percentage	30.0%	41.3%	33.3%	23.5%	30.5%	26.4%	23.6%	31.8%	29.0%	29.0%
Receiving drug therapy										
Estimated number (million)	0.4	0.1	0.5	1.0	0.5	1.6	0.3	0.8	1.1	3.1
Percentage	3.3%	2.2%	2.9%	6.7%	4.7%	5.9%	9.6%	14.3%	12.7%	6.1%
Receiving no treatment										
Estimated number (million)	7.4	2.6	10.0	11.0	7.1	18.0	1.9	3.0	4.9	33.0
Percentage	66.8%	56.5%	63.7%	69.8%	64.9%	67.8%	66.8%	53.9%	58.3%	65.0%

Low-density cholesterol reduction required: In Table V, we examine the percent reduction in LDL cholesterol required by people qualifying for drug therapy according to the ATP II guidelines based on observed LDL cholesterol levels. Of all people qualifying for drug therapy, 40.4% (an estimated 8.5 million people) require a reduction in LDL cholesterol levels of >30% to reach their treatment goal. Among those with coronary heart disease who qualify for drug therapy, 74.8% required a reduction in LDL cholesterol of >30%. Those without coronary heart disease who are eligible for drug treatment are less likely to require >30% reductions in LDL cholesterol to meet ATP II treatment goals; however, 55.4% of the people in this group require a reduction of >30% to reach the desirable LDL cholesterol level of ≤130 mg/dl.

Discussion

NHANES III Phase 2 data provide the latest source of information on the distribution of LDL cholesterol levels in U.S. adults. Based on this nationally representative sample, >28% of U.S. adults and >82% of U.S. adults with coronary heart disease are eligible for treatment based on ATP II guidelines. The relation between elevated LDL cholesterol levels and increased coronary heart disease morbidity and mortality has been well established.[4–8] Because coronary heart disease results in about 500,000 deaths annually in the U.S., elevated LDL cholesterol levels are a public health problem that requires serious attention, and prompt diagnosis and effective

treatment of elevated LDL cholesterol levels may substantially reduce coronary heart disease mortality as well as reduce related health care expenditures.

TABLE V Reduction in Low-Density Lipoprotein Cholesterol Required to Meet Adult Treatment Panel II Treatment Goal or Desired Level for Those Who Qualify for Drug Treatment

	Coronary Heart Disease Risk Group				
	Without Coronary Heart Disease			Coronary Heart Disease—to Reach Treatment Goal and Desired Level ≤100 mg/dl	All to Reach Treatment Goal
	With <2 Risk Factors to Reach Treatment Goal <160 mg/dl	With ≥2 Risk Factors to Reach Treatment Goal <130 mg/dl	All to Reach Desired Level of <130 mg/dl		
Estimated number in risk group who qualify for drug therapy (millions)	4.7	11.0	15.7	5.5	21.2
Require >30% reduction					
Estimated number (millions)	0.4	4.0	8.7	4.1	8.5
Percentage	9.1%	36.5%	55.4%	74.8%	40.4%

Our findings indicate that most U.S. adults eligible for cholesterol-lowering therapy report that they do not receive treatment. Only about 35% of treatment eligible persons report that they receive dietary or drug therapy. Even among patients with coronary heart disease who are eligible for drug therapy, over half report that they receive no therapy. In NHANES, treatment prevalence is self-reported by patients and no attempt was made to confirm treatment by reviewing medical records. Still, these results suggest that many patients with elevated LDL levels remain untreated.

For those who are treated, recent research casts doubt on the ability of dietary therapy to produce sizable reductions in LDL cholesterol, particularly if the therapy is not accompanied by intensive counseling.[9,10] Among drug therapies, bile acid sequestrants are expected to reduce LDL cholesterol by 15% to 20%, and 3-hydroxy-3methylglutaryl coenzyme A reductase inhibitors are expected to reduce LDL cholesterol by 20% to 60% depending on the agent and dose chosen.[11] However, a number of recent studies indicate that, even when drug therapy is prescribed, a considerable percentage of people treated do not reach their target LDL cholesterol levels. Less than half of patients with LDL cholesterol >160 mg/dl achieved target lipid levels.[12] Among those with heart disease, only 30% of patients achieved ATP II goals after treatment with fluvastatin at 20 mg,[13] and only 24% of patients reached their goals after treatment with 3-hydroxy-3methylglutaryl coenzyme A reductase inhibitors.[14] In a 2.5-year study, 70% of patients with coronary heart disease and baseline LDL cholesterol levels >130 mg/dl needed combination therapy to reach ATP II goals.[15] Another study found that only 38% of patients currently undergoing treatment for hypercholesterolemia were meeting their ATP II treatment goal.[16]

Our results show that a large percentage of people who qualify for drug treatment require substantial reductions in LDL cholesterol levels. Forty percent of all persons who qualify for drug treatment require at least a 30% reduction in LDL cholesterol; nearly 75% of those with coronary heart disease who qualify for drug treatment need at least a 30% reduction in LDL cholesterol. For a patient group often treated with drugs, middle-aged men aged 45 to 64 years with coronary heart disease, 80% of the population eligible for drug treatment requires at least a

30% reduction in LDL cholesterol. Thus, our findings provide at least a partial explanation for why many individuals receiving therapy do not reach their treatment goals; they require a larger reduction in LDL cholesterol than many therapies can provide.

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